Clinical trial results:
Randomized, Open Label, Multicenter Study Assessing The Clinical Benefit Of Isatuximab Combined With Carfilzomib (Kyprolis®) And Dexamethasone Versus Carfilzomib With Dexamethasone In Patients With Relapse And/Or Refractory Multiple Myeloma Previously Treated With 1 to 3 Prior Lines

Summary

EudraCT number	2017-001940-37
Trial protocol	GB CZ HU ES FR GR IT
Global end of trial date	03 January 2025
Results information	
Result version number	v3 (current)
This version publication date	07 January 2026
First version publication date	11 May 2023
Version creation reason	

Trial information

Trial identification	
Sponsor protocol code	EFC15246
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03275285
WHO universal trial number (UTN)	U1111-1195-5957
Other trial identifiers	IND Number: 103217

Notes:

Sponsors	
Sponsor organisation name	Sanofi Aventis Recherche & Développement
Sponsor organisation address	82, avenue Raspail, GENTILLY, France, 94250
Public contact	Trial Transparency Team, Sanofi Aventis Recherche & Développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 January 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the benefit of isatuximab in combination with carfilzomib and dexamethasone in the prolongation of progression free survival (PFS) using International Myeloma Working Group (IMWG) as compared to carfilzomib and dexamethasone in subjects with relapsed and/or refractory multiple myeloma (MM) previously treated with 1 to 3 lines of therapy.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial, as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 20
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Türkiye: 14
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Australia: 37
Country: Number of subjects enrolled	Brazil: 33
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czechia: 34
Country: Number of subjects enrolled	France: 39

Worldwide total number of subjects	302
EEA total number of subjects	136

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	154
From 65 to 84 years	146
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Study conducted at 69 active centers in 16 countries. 341 subjects screened between 25 Oct 2017 & 21 Mar 2019, 39 subjects were screen failure - not met eligibility criteria. Reason for not completed = Reason for definitive treatment discontinuation.

Pre-assignment

Screening details:

Data cut-off date for result analysis reported 07Feb2020 (efficacy outcomes), 14Jan2022 (CR, MRD, PFS2), 7Feb2020 (Primary analysis of PFS i.e., interim analysis conducted at 103 events, (14Jan2022) final analysis of PFS conducted at 159 events, 7Feb2023 (overall survival), and 3Jan2025 (LPLV).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Carfilzomib + Dexamethasone (Kd)

Arm description:

Subjects received carfilzomib 20 milligrams per meter square (mg/m^2), intravenous (IV) infusion on Days 1, and 2 in Cycle 1, and then escalated to 56 mg/m^2 on Days 8, 9, 15 and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15 and 16 of each subsequent 28-day treatment cycle along with dexamethasone 20 milligrams (mg), orally (PO) or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle until disease progression or unacceptable adverse event or subject’s decision to discontinue the study treatment or any other reason, whichever comes first.

Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Dexamethasone 20 mg was administered PO or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle along with Carfilzomib.

Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	Kyprolis
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carfilzomib 20 mg/m^2, was administered as an IV infusion on Days 1, and 2 in Cycle 1, and then escalated to 56 mg/m^2 on Days 8, 9, 15 and 16 of Cycle 1 and then on Days 1, 2, 8, 9, 15 and 16 of each subsequent 28-day treatment cycle along with dexamethasone 20 mg, PO or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle.

Arm title	Isatuximab + Carfilzomib + Dexamethasone (IKd)

Arm description:

Subjects received isatuximab 10 mg/kg, IV infusion on Days 1, 8, 15 and 22 in Cycle 1, and then on Days 1 and 15 of each 28-day treatment cycle along with carfilzomib 20 mg/m^2, IV on Days 1, and 2 in Cycle 1, and then escalated to 56 mg/m^2 on Days 8, 9, 15 and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15 and 16 of each subsequent 28-day treatment cycle and dexamethasone 20 mg, PO or IV on Day 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle until disease progression or unacceptable adverse event or subject’s decision to discontinue the study treatment or any other reason, whichever

comes first.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	Kyprolis
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carfilzomib 20 (mg/m^2, was administered as an IV infusion on Days 1, and 2 in Cycle 1, and then escalated to 56 mg/m^2 on Days 8, 9, 15 and 16 of Cycle 1 and then on Days 1, 2, 8, 9, 15 and 16 of each subsequent 28-day treatment cycle along in combination with carfilzomib and dexamethasone.

Investigational medicinal product name	Isatuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Isatuximab 10 mg/kg, was administered as an IV infusion on Days 1, 8, 15 and 22 in Cycle 1, and then on Days 1 and 15 of each 28-day treatment cycle in combination with carfilzomib and dexamethasone.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Dexamethasone 20 mg was administered PO or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle along with carfilzomib and isatuximab.

Number of subjects in period 1	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)
Started	123	179
Treated	122	177
Completed	0	0
Not completed	123	179
Adverse Event	24	29
Randomized and not treated	1	2
Other	10	12
Study discontinuation	1	5
Treatment extension study	1	24
Progressive disease	68	86
Withdrawal by subject	18	21

Baseline characteristics

Reporting groups	
Reporting group title	Carfilzomib + Dexamethasone (Kd)
Reporting group description:	
Subjects received carfilzomib 20 milligrams per meter square (mg/m^2), intravenous (IV) infusion on Days 1, and 2 in Cycle 1, and then escalated to 56 mg/m^2 on Days 8, 9, 15 and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15 and 16 of each subsequent 28-day treatment cycle along with dexamethasone 20 milligrams (mg), orally (PO) or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle until disease progression or unacceptable adverse event or subject's decision to discontinue the study treatment or any other reason, whichever comes first.	
Reporting group title	Isatuximab + Carfilzomib + Dexamethasone (IKd)
Reporting group description:	
Subjects received isatuximab 10 mg/kg, IV infusion on Days 1, 8, 15 and 22 in Cycle 1, and then on Days 1 and 15 of each 28-day treatment cycle along with carfilzomib 20 mg/m^2, IV on Days 1, and 2 in Cycle 1, and then escalated to 56 mg/m^2 on Days 8, 9, 15 and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15 and 16 of each subsequent 28-day treatment cycle and dexamethasone 20 mg, PO or IV on Day 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle until disease progression or unacceptable adverse event or subject's decision to discontinue the study treatment or any other reason, whichever comes first.	

Reporting group values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)	Total
Number of subjects	123	179	302
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.9	63.3	
standard deviation	± 10.0	± 9.8	-
Gender categorical Units: Subjects			
Female	55	78	133
Male	68	101	169
Race Units: Subjects			
White	83	131	214
Black or African American	4	5	9
Asian	24	26	50
Missing/Not reported	12	14	26
Multiple	0	3	3

End points

End points reporting groups

Reporting group title	Carfilzomib + Dexamethasone (Kd)

Reporting group description:

Subjects received carfilzomib 20 milligrams per meter square (mg/m^2), intravenous (IV) infusion on Days 1, and 2 in Cycle 1, and then escalated to 56 mg/m^2 on Days 8, 9, 15 and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15 and 16 of each subsequent 28-day treatment cycle along with dexamethasone 20 milligrams (mg), orally (PO) or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle until disease progression or unacceptable adverse event or subject's decision to discontinue the study treatment or any other reason, whichever comes first.

Reporting group title	Isatuximab + Carfilzomib + Dexamethasone (IKd)

Reporting group description:

Subjects received isatuximab 10 mg/kg, IV infusion on Days 1, 8, 15 and 22 in Cycle 1, and then on Days 1 and 15 of each 28-day treatment cycle along with carfilzomib 20 mg/m^2, IV on Days 1, and 2 in Cycle 1, and then escalated to 56 mg/m^2 on Days 8, 9, 15 and 16 of Cycle 1 and on Days 1, 2, 8, 9, 15 and 16 of each subsequent 28-day treatment cycle and dexamethasone 20 mg, PO or IV on Day 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle until disease progression or unacceptable adverse event or subject's decision to discontinue the study treatment or any other reason, whichever comes first.

Primary: Progression Free Survival as Determined by Independent Response Committee: Final Analysis

End point title	Progression Free Survival as Determined by Independent Response Committee: Final Analysis

End point description:

PFS: time (in months) from randomisation to date of first documentation of PD or date of death from any cause, whichever comes first. If PD and death was not observed before analysis cut-off date or date of initiation of further anti-myeloma treatment, PFS was censored at date of last valid disease assessment or analysis cut-off date, whichever comes first. PD as per IMWG criteria: any 1 of following: Inc of >=25% in Serum M-component from nadir; serum M component increase >=1 g/dL in 2 consecutive assessment, if starting M component was >=5 g/dL; and/or inc of >=25% in Urine M-component from nadir and/or development of new bone lesion/soft tissue extramedullary disease/inc >=50% from nadir in sum of perpendicular diameters of existing soft tissue extramedullary disease lesion if >1 lesion/ >=50% inc in longest diameter of previous soft tissue extramedullary disease lesion >1 cm in short axis. Analysis was performed on ITT population and estimated by Kaplan-Meier method.

End point type	Primary

End point timeframe:

From randomisation until the final analysis data cut-off date of 14 January 2022 (the median duration of follow-up was 43.96 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	19.15 (15.770 to 25.035)	35.65 (25.758 to 43.959)		

Statistical analyses

Statistical analysis title	PFS per IRC: Final Analysis

Statistical analysis description:

Statistical Analysis Progression Free Survival: Final Analysis between Carfilzomib - Dexamethasone (Kd) and Isatuximab, Carfilzomib and Dexamethasone (IKd) arms.

Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.576
Confidence interval	
level	95.4 %
sides	2-sided
lower limit	0.418
upper limit	0.792

Notes:

[1] - Hazard Ratio was stratified on number of prior lines of therapy (1 vs. >1) and R-ISS stage (I or II vs. III vs. not classified) according to IRT.

Primary: Progression Free Survival (PFS) As Determined by Independent Response Committee (IRC): Primary Analysis

End point title	Progression Free Survival (PFS) As Determined by Independent Response Committee (IRC): Primary Analysis

End point description:

Time from randomisation to date of 1st documentation of progressive disease (PD)/date of death, whichever 1st. If PD & death not observed before cut-off date/date of initiation of further anti-myeloma treatment, PFS censored at date of last valid disease assessment not showing PD performed prior to initiation of further anti-myeloma treatment/cut-off date, whichever 1st. PD:any 1 of following: increase(inc) >=25% serum M-component from nadir; serum M component inc >=1 g/dL in 2 consecutive assessment, if starting M component >=5 g/dL and/or inc >=25% in urine M-component from nadir and/or development of new bone lesion/soft tissue extramedullary disease/inc >=50% from nadir in sum of perpendicular diameter of existing soft tissue extramedullary disease lesion if >1 lesion/ >=50% increase in longest diameter of previous soft tissue extramedullary disease lesion >1 cm in short axis. ITT population. Kaplan-Meier method.99999=value could not be calculated as <50% subjects had PFS events.

End point type	Primary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	19.15 (15.770 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	PFS per IRC: Primary Analysis

Statistical analysis description:

Statistical analysis for comparison of PFS between the Kd and IKd arms based on primary analysis.

Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0007 [3]
Method	Stratified Log-Rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.531
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.318
upper limit	0.889

Notes:

[2] - For PFS, the nominal significance levels at primary analysis was determined using alpha-spending function in order to control overall 1-sided type 1 error at 2.5%. The 1-sided nominal significance level to declare overwhelming efficacy at primary analysis (103 PFS events) was 0.005. Because the median PFS was not reached at the primary analysis, it was described at the final analysis.

[3] - One-sided p-value based on Stratified log-rank test. Threshold for significance=0.005. Stratified on number of prior lines of therapy(1 vs >1) & revised international staging system (I/II vs III vs not classified) per interactive response technology.

Primary: Progression Free Survival as Determined by Independent Response Committee: (Event Censored if Occurred >8 Weeks From Last Disease Assessment): Primary Analysis

End point title	Progression Free Survival as Determined by Independent Response Committee: (Event Censored if Occurred >8 Weeks From Last Disease Assessment): Primary Analysis

End point description:

Time from randomisation to date of 1st PD documentation/death, whichever 1st. If PD & death not observed before cut-off date/date of further anti-myeloma treatment, PFS censored at date of last disease assessment not showing PD performed prior to initiation of further anti-myeloma treatment/cut-off date, whichever 1st. Progression/death occurring >8 week after last disease assessment censored at earliest date of last disease assessment without evidence of progression before initiation of anti-myeloma treatment & cut-off date. PD:meeting any 1: Inc >=25% in Serum M-component from nadir; serum M component inc >=1 g/dL in 2 consecutive assessment; and/or inc >=25% in Urine M-component from nadir and/or development of new bone lesion/soft tissue extramedullary disease/inc >=50% from nadir in sum of perpendicular diameter of existing soft tissue extramedullary disease lesion. ITT population. Kaplan-Meier method. 99999=value could not be calculated as <50% subjects had PFS events.

End point type	Primary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (the median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	20.27 (15.770 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	PFS: Event Censored: Primary Analysis

Statistical analysis description:

Statistical analysis for comparison of PFS between the Kd and IKd arm based on primary analysis.

Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0016 [5]
Method	Stratified Log-Rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.548
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	0.317
upper limit	0.948

Notes:

[4] - The 1-sided nominal significance level to declare overwhelming efficacy at primary analysis was 0.004. Because the median PFS was not reached at the primary analysis, it was described at the final analysis.

[5] - One-sided p-value based on Stratified log-rank test. Threshold for statistical significance at 0.004. Stratified on number of prior lines of therapy (1 vs >1) & revised international staging system stage (I/II vs III vs not classified) as per IRT.

Primary: Progression Free Survival as Determined by Independent Response Committee (Event Censored if Occurred >8 Weeks From Last Disease Assessment): Final Analysis

End point title	Progression Free Survival as Determined by Independent Response Committee (Event Censored if Occurred >8 Weeks From Last Disease Assessment): Final Analysis

End point description:

Time from randomisation to date of 1st documentation of PD/date of death any cause, whichever come 1st. If PD & death not observed before cut-off date/date of initiation of further anti-myeloma treatment,

PFS censored at date of last valid disease assessment not showing PD/cut-off date, whichever is 1st. Progressions/deaths occurring >8 weeks after last disease assessment censored at earliest date of last valid disease assessment not showing PD before initiation of further anti-myeloma treatment & cut-off date. PD: meeting any 1 criteria: Inc of >=25% in serum M-component from nadir; serum M component inc >=1 g/dL in 2 consecutive assessment; and/or inc of >=25% in urine M-component from nadir and/or development of new bone lesion/soft tissue extramedullary disease/inc >=50% from nadir in sum of perpendicular diameters of existing soft tissue extramedullary disease lesion. ITT population. Kaplan-Meier method. 99999=value could not be calculated as <50% subjects had PFS events.

End point type	Primary

End point timeframe:

From randomisation until the final analysis data cut-off date of 14 Jan 2022 (the median duration of follow-up was 43.96 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	20.76 (16.164 to 28.189)	41.66 (27.138 to 99999)		

Statistical analyses

Statistical analysis title	PFS: Event Censored: Final Analysis
Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.594
Confidence interval	
level	95.4 %
sides	2-sided
lower limit	0.424
upper limit	0.832

Notes:

[6] - Hazard Ratio was stratified on number of prior lines of therapy (1 vs. >1) and R-ISS stage (I or II vs. III vs. not classified) according to IRT.

Secondary: Percentage of Subjects With Overall Response (OR) as Determined by Independent Response Committee: Primary Analysis

End point title	Percentage of Subjects With Overall Response (OR) as Determined by Independent Response Committee: Primary Analysis

End point description:

OR: subjects with sCR, CR, VGPR & partial response (PR) as best overall response assessed using IMWG response criteria (from start of treatment until disease progression, death, initiation of further anti-myeloma treatment/cutoff date, whichever is 1st). sCR: negative immunofixation on serum & urine, disappearance of soft tissue plasmacytoma, <5% plasma cells in bone marrow aspirate (BMA) + normal

FLC ratio (0.26-1.65), absence of clonal cells in bone marrow biopsy. CR: negative immunofixation on serum & urine, disappearance of soft tissue plasmacytoma, <5% plasma cells in BMA. VGPR: serum & urine M-protein detectable by immunofixation, not on electrophoresis/,>=90% reduction in serum M-protein + urine M-protein level <100mg/24h/,>=90% decrease in SPD compared to baseline in plasmacytoma. PR:>=50% reduction of serum M-protein & decrease in 24h urinary M-protein by >=90%/<200mg/24h, if present at baseline,>=50% decrease in SPD of soft tissue plasmacytoma. Analysis on ITT population.

End point type	Secondary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (the median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: percentage of subjects				
number (not applicable)	82.9	86.6		

Statistical analyses

Statistical analysis title	Percentage of Subjects with OR

Statistical analysis description:

Statistical analysis for comparison of Overall Response between the Kd and IKd arms based on primary analysis.

Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.193 [8]
Method	Cochran-Mantel-Haenszel

Notes:

[7] - A closed test procedure was used to control the Type I error rate from the primary efficacy endpoints sequentially through the secondary efficacy endpoints. No further testing would be performed unless the significance level had been reached on PFS and testing on subsequent endpoints were continued only if the null hypothesis for the previously tested endpoint was rejected.

[8] - One-sided p-value based on Stratified Cochran-Mantel-Haenszel test. One sided p-value was stratified based on randomisation factors according to IRT. Threshold for statistical significance level at 0.025.

Secondary: Percentage of Subjects With Very Good Partial Response (VGPR) or Better as Determined by Independent Response Committee: Primary Analysis

End point title	Percentage of Subjects With Very Good Partial Response (VGPR) or Better as Determined by Independent Response Committee: Primary Analysis

End point description:

VGPR or better: defined as subjects with sCR, CR and VGPR as the best overall response (defined as best response from start of treatment until disease progression, death, initiation of further anti-myeloma treatment or cut-off date whichever occurs first) as per IRC. As per IMWG response criteria: sCR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in BMAs plus normal free light chain (FLC) ratio (0.26-1.65), absence of clonal cells in

bone marrow biopsy. CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in BMAs. VGPR: serum and urine M-protein detectable by immunofixation, not on electrophoresis/,>=90% reduction in serum M-protein plus urine M-protein level <100mg/24h/,>=90% decrease in SPD compared to baseline in soft tissue plasmacytoma. ITT population: subjects who gave their informed consent & for whom there was confirmed randomisation number by IRT.

End point type	Secondary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (the median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: percentage of subjects				
number (not applicable)	56.1	72.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With VGPR or Better with Minimal Residual Disease (MRD) Negativity: Primary Analysis

End point title	Percentage of Subjects With VGPR or Better with Minimal Residual Disease (MRD) Negativity: Primary Analysis

End point description:

Percentage of subjects with sCR, CR and VGPR for whom MRD assessed by sequencing was negative at any time after first dose of study treatment. MRD was assessed centrally by next-generation sequencing in bone marrow aspiration samples from subjects who achieve VGPR or better, to determine depth of response at molecular level. VGPR or better: percentage of subjects with sCR, CR and VGPR. sCR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in BMAs plus normal FLC ratio (0.26-1.65), absence of clonal cells in bone marrow biopsy. CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in BMAs. VGPR: serum and urine M-protein detectable by immunofixation, not on electrophoresis/,>=90% reduction in serum M-protein plus urine M-protein level <100mg/24h/,>=90% decrease in SPD compared to baseline in soft tissue plasmacytoma. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (the median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: percentage of subjects				
number (not applicable)	13.0	29.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Complete Response With MRD Negativity: Final Analysis

End point title	Percentage of Subjects With Complete Response With MRD Negativity: Final Analysis

End point description:

MRD negativity: percentage of subjects for whom MRD was negative by next-generation sequencing at any timepoint after 1st dose of study treatment. Threshold for negativity is 10^-5. MRD status in a subject was negative if at least 1 result of assessment was negative in subject otherwise MRD was considered as positive (MRD status reported as positive, missing or unevaluable). CR: subjects with sCR and CR. IMWG response criteria for sCR: negative immunofixation on serum & urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in bone marrow aspirates plus normal FLC ratio (0.26-1.65), absence of clonal cells in bone marrow biopsy. CR: negative immunofixation on serum & urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in bone marrow aspirates. Complete response at time of the final analysis was assessed with Hydrashift isatuximab IFE assay, which separated IgG isatuximab from IgG M protein. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomisation until the final analysis data cut-off date of 14 Jan 2022 (the median duration of follow-up was 43.96 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: percentage of subjects				
number (not applicable)	12.2	26.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With VGPR or Better With Minimal Residual Disease (MRD) Negativity: Final Analysis

End point title	Percentage of Subjects With VGPR or Better With Minimal

	Residual Disease (MRD) Negativity: Final Analysis

End point description:

Percentage of subjects with sCR, CR and VGPR for whom MRD assessed by sequencing was negative at any time after first dose of study treatment. MRD was assessed centrally by next-generation sequencing in BM aspiration samples from subjects who achieve VGPR/better, to determine depth of response at molecular level. VGPR or better: percentage of subjects with sCR, CR and VGPR. sCR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in bone marrow aspirates plus normal FLC ratio, absence of clonal cells in bone marrow biopsy. CR: negative immunofixation on serum & urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in bone marrow aspirates. VGPR: serum & urine M-protein detectable by immunofixation, not on electrophoresis/,>=90% reduction in serum M-protein plus urine M-protein level <100mg/24h/,>=90% decrease in SPD compared to baseline in soft tissue plasmacytoma. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomisation until the final analysis data cut-off date of 14 Jan 2022 (the median duration of follow-up was 43.96 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: percentage of subjects				
number (not applicable)	13.8	33.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Complete Response (CR) as per Independent Response Committee: Final Analysis

End point title	Percentage of Subjects with Complete Response (CR) as per Independent Response Committee: Final Analysis

End point description:

Complete response was defined as the subjects with sCR and CR. IMWG response criteria for sCR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in bone marrow aspirates plus normal FLC ratio (0.26-1.65), absence of clonal cells in bone marrow biopsy. CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, <5% plasma cells in bone marrow aspirates. Complete response at the time of the final analysis was assessed with hydrashift isatuximab immunofixation electrophoresis (IFE) assay, which separated immunoglobulin G (IgG) isatuximab from IgG M protein. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomisation until the final analysis data cut-off date of 14 Jan 2022 (the median duration of follow-up was 43.96 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: percentage of subjects				
number (not applicable)	28.5	44.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP): Primary Analysis

End point title	Time to Progression (TTP): Primary Analysis

End point description:

Time from randomisation to date of 1st documentation of PD. If progression not observed before analysis cut-off date/date of initiation of further anti-myeloma treatment, TTP censored at date of last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment (if any)/analysis cut-off date, whichever 1st. As per IMWG criteria, PD was defined for subjects with inc of >= 25% from lowest confirmed value in any one of the following criteria: serum M-protein (the absolute inc must be >= 0.5 g/dL), serum M-protein inc >=1 g/dL if the lowest M component was >=5 g/dL; urine M-component (the absolute inc must be >=200 mg/24hour), appearance of new lesion(s), >=50% inc from nadir in SPD of >1 lesion, or >=50% inc in the longest diameter of a previous lesion >1 centimeter in short axis. Analysis performed on ITT population using Kaplan-Meier method. 99999 = value not calculated due to less number of subjects with progression events.

End point type	Secondary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (the median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	20.27 (16.986 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis TTP: Primary Analysis
Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[9]
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.495
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.324
upper limit	0.757

Notes:

[9] - Stratification was done on the number of prior lines of therapy (1 vs. >1) and R-ISS stage (I or II vs. III vs. not classified) according to IRT.

Secondary: Overall Survival (OS): Final Analysis

End point title	Overall Survival (OS): Final Analysis

End point description:

Overall survival, defined as the time from the date of randomization to death from any cause. The data reported is based on cut-off date of 7 Feb 2023. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 7 Feb 2023 (the median duration of follow-up was 56.61 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123[10]	179[11]		
Units: months				
median (confidence interval 95%)	50.60 (38.932 to 99999)	99999 (52.172 to 99999)		

Notes:

[10] - 9999: upper limit of confidence interval could not be reached due to less number of subjects

[11] - 9999: median, upper & lower limits of confidence interval not calculated due to less 50% of subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR): Primary Analysis

End point title	Duration of Response (DOR): Primary Analysis

End point description:

Time from date of 1st IRC determined response for subject achieving PR/better to date of 1st documented PD determined by IRC/death, whichever is 1st. If disease progression/death before analysis cut-off date not observed, DOR censored at date of last valid disease assessment performed prior to initiation of further anti-myeloma treatment/data cut-off date, whichever 1st. PD:inc >=25% from lowest confirmed value in any 1 of following criteria:serum M-protein (absolute inc >=0.5 g/dL), serum M-protein inc >=1g/dL if lowest M component >=5g/dL; urine M-component (absolute inc >=200mg/24 hour),appearance of new lesion, >=50% inc from nadir in SPD of >1 lesion, >=50% inc in longest diameter of previous lesion >1 cm in short axis. PR: >=50% reduction of serum M-protein & reduction in 24h urinary M-protein by >=90%/<200mg/24 h. Analysis on subset of subjects with PR/better in ITT

population by Kaplan Meier method. 99999=value not calculated as <50% subject reaching PR/better with PFS event.

End point type	Secondary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (the median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	155		
Units: months				
median (confidence interval 95%)	99999 (14.752 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis for DOR: Primary Analysis
Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority[12]
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.269
upper limit	0.672

Notes:

[12] - Stratification was done on the number of prior lines of therapy (1 vs. >1) and R-ISS stage (I or II vs. III vs. not classified) according to IRT.

Secondary: Time to Best Response (TBR): Primary Analysis

End point title	Time to Best Response (TBR): Primary Analysis

End point description:

Time to best response: time (in months) from randomisation to date of 1st occurrence of IRC determined as best overall response (PR/better) that is subsequently confirmed. In absence of response, subjects were censored at earliest date of last valid disease assessment before disease progression/death, date of last valid disease assessment before initiation of further anti-myeloma treatment (if any)/ analysis cut-off date, whichever was 1st. PR (IMWG criteria) was defined as >=50% reduction of serum M-protein & reduction in 24 hours urinary M-protein by >=90% or to <200 mg/24 h. Additionally, if present at baseline, a >=50% reduction in size (SPD) of soft tissue plasmacytomas was also required. Best Overall Response defined as best response, using IRC's assessment of response, from start of treatment until disease progression, death, initiation of further anti-myeloma treatment or cut-off date, whichever occurs 1st. Analysis was performed on ITT population using Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (the median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	3.78 (2.858 to 4.172)	4.60 (3.811 to 5.257)		

Statistical analyses

Statistical analysis title	Stat Analysis for TBR: Primary Analysis
Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[13]
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.955
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.233

Notes:

[13] - Stratification was done on the number of prior lines of therapy (1 vs. >1) and R-ISS stage (I or II vs. III vs. not classified) according to IRT.

Secondary: Time to First Response (TFR): Primary Analysis

End point title	Time to First Response (TFR): Primary Analysis

End point description:

Time to first response was defined as the time (in months) from randomisation to the date of first IRC determined response (PR or better) that is subsequently confirmed. In the absence of response, subjects were censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first. PR per IMWG criteria was defined as >=50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >=90% or to <200 mg/24 h. In addition to the above listed criteria, if present at baseline, a >=50% reduction in the size (SPD) of soft tissue plasmacytomas was also required. Analysis was performed on ITT population. Analysis was performed by Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From randomisation until the primary analysis data cut-off date of 7 Feb 2020 (the median duration of follow-up was 20.73 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	1.12 (1.051 to 1.183)	1.08 (1.051 to 1.117)		

Statistical analyses

Statistical analysis title	Statistical Analysis for TFR: Primary Analysis
Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[14]
Parameter estimate	Stratified Hazard Ratio
Point estimate	1.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.888
upper limit	1.471

Notes:

[14] - Stratification was done on the number of prior lines of therapy (1 vs. >1) and R-ISS stage (I or II vs. III vs. not classified) according to IRT.

Secondary: Health Related Quality of Life (HRQL): Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 30 Items (EORTC QLQ-C30): Global Health Status Score at Specified Timepoints

End point title	Health Related Quality of Life (HRQL): Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 30 Items (EORTC QLQ-C30): Global Health Status Score at Specified Timepoints

End point description:

EORTC QLQ-C30 is a cancer-specific instrument that contains 30 items & provides multidimensional assessment of HRQL. EORTC QLQ-C30 includes global health status/quality of life (GHS/QOL), functional scales (physical, role, cognitive, emotional, social), symptom scales (fatigue, pain, nausea/vomiting), and 6 single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, financial difficulties). Most questions from QLQ-C30 are 4-point scale (1/Not at All to 4/Very Much), except Items 29-30, which comprise GHS scale & are 7-point scale (1/Very Poor to 7/Excellent). GHS total score is calculated as ([{Q29+Q30}/2]-1)/6*100. Answers are converted into grading scale, with values between 0 (worse outcome) to100 (best outcome). High score represents a favorable outcome with best quality of life for subject. Results reported for primary analysis with data cut-off date 7-Feb-2020. Analysis was performed on ITT population. 'n' signifies subjects with available data for each category.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle (Cycle 2 to Cycle 25), at the End of Treatment visit (any day up to 114

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=99,151)	1.52 (± 21.11)	-1.60 (± 20.06)		
Cycle 3 Day 1 (n=100,154)	4.17 (± 22.92)	0.05 (± 20.29)		
Cycle 4 Day 1 (n=100, 150)	3.58 (± 21.20)	-1.89 (± 23.71)		
Cycle 5 Day 1 (n=95, 149)	3.60 (± 21.80)	-1.23 (± 23.12)		
Cycle 6 Day 1 (n=88, 145)	3.13 (± 20.50)	-1.44 (± 22.12)		
Cycle 7 Day 1 (n=85, 141)	4.22 (± 22.55)	-1.77 (± 22.38)		
Cycle 8 Day 1 (n=83, 134)	3.82 (± 21.71)	-1.06 (± 20.78)		
Cycle 9 Day 1 (n=77, 128)	6.60 (± 19.28)	-0.78 (± 22.17)		
Cycle 10 Day 1 (n=73, 124)	4.91 (± 21.55)	-1.21 (± 20.35)		
Cycle 11 Day 1 (n=71, 121)	4.34 (± 20.06)	-1.10 (± 20.18)		
Cycle 12 Day 1 (n=64, 119)	8.59 (± 22.37)	0.84 (± 22.40)		
Cycle 13 Day 1 (n=60, 112)	7.08 (± 19.76)	-1.26 (± 20.63)		
Cycle 14 Day 1 (n=59, 111)	9.75 (± 21.62)	-0.98 (± 21.43)		
Cycle 15 Day 1 (n=57, 103)	5.26 (± 22.14)	0.16 (± 20.51)		
Cycle 16 Day 1 (n=50, 101)	6.33 (± 20.73)	-1.07 (± 20.94)		
Cycle 17 Day 1 (n=47, 99)	7.27 (± 21.04)	0.00 (± 22.18)		
Cycle 18 Day 1 (n=45, 92)	8.70 (± 23.16)	-0.36 (± 20.56)		
Cycle 19 Day 1 (n=41, 88)	12.40 (± 21.42)	-1.23 (± 20.12)		
Cycle 20 Day 1 (n=34, 87)	10.78 (± 20.97)	-1.05 (± 20.40)		
Cycle 21 Day 1 (n=28, 72)	12.50 (± 21.81)	-1.85 (± 21.54)		
Cycle 22 Day 1 (n=19, 53)	17.98 (± 22.27)	0.31 (± 21.24)		
Cycle 23 Day 1 (n=15, 37)	15.56 (± 22.02)	3.15 (± 20.73)		
Cycle 24 Day 1 (n=9, 22)	14.81 (± 26.28)	0.38 (± 14.88)		
Cycle 25 Day 1 (n=5, 16)	15.00 (± 28.50)	3.13 (± 17.18)		
End of Treatment (n=57,56)	-6.14 (± 22.90)	-11.90 (± 25.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Second Progression Free Survival (PFS2): Final Analysis - Data Cut-off Date of 14 Jan 2022

End point title	Second Progression Free Survival (PFS2): Final Analysis - Data Cut-off Date of 14 Jan 2022

End point description:

Time from date of randomisation to date of 1st documentation of PD (assessed by investigator) after initiation of further anti-myeloma treatment /death (any cause), whichever 1st. Subjects alive without progression after initiation of further anti-myeloma treatment before analysis cut-off date, PFS2 censored at date of last follow-up visit not showing disease progression after initiation of further anti-myeloma treatment/analysis cut-off date, whichever 1st. Per IMWG,PD: defined for subjects with increase (inc) of >= 25% from lowest confirmed value in any 1 of criteria: serum M-protein (absolute inc must be >= 0.5 g/dL), serum M-protein inc >=1 g/dL if lowest M component was >=5 g/dL; urine M-component (absolute inc >=200 mg/24hour), appearance of new lesion(s), >=50% inc from nadir in SPD of >1 lesion, or >=50% inc in longest diameter of previous lesion >1 centimeter short axis. ITT population, Kaplan-Meier method, 99999=value not calculated as not enough subjects with PFS2 events.

End point type	Secondary

End point timeframe:

From randomisation until the final analysis data cut-off date of 14 Jan 2022 (the median duration of follow-up was 43.96 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	35.58 (24.049 to 40.509)	47.18 (38.111 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS2: Final Analysis
Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[15]
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.683
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.496
upper limit	0.941

Notes:

[15] - Stratification was done on the number of prior lines of therapy (1 vs. >1) and R-ISS stage (I or II vs. III vs. not classified) according to IRT.

Secondary: Second Progression Free Survival (PFS2): Final Analysis - Data Cut-off Date of 07 Feb 2023

End point title	Second Progression Free Survival (PFS2): Final Analysis - Data Cut-off Date of 07 Feb 2023

End point description:

PFS2 defined as time (in months) from date of randomization to date of 1st documentation of PD (as assessed by investigator) after initiation of further anti-myeloma treatment/death from any cause, whichever comes 1st.Participants alive without progression after initiation of further anti-myeloma treatment before analysis cut-off date,PFS2 censored at date of last follow-up visit not showing disease progression after initiation of further anti-myeloma treatment /analysis cut-off date,whichever comes 1st.As per IMWG criteria, PD:defined for participants with increase of >= 25% from lowest confirmed value in any 1 of following criteria: serum M-protein (absolute increase must be >= 0.5 g/dL), serum M-protein increase >=1 g/dL if lowest M component was >=5 g/dL; urine M-component (absolute increase must be >=200 mg/24hour), appearance of new lesion(s), >=50% increase from nadir in SPD of >1 lesion, or >=50% increase in longest diameter of previous lesion >1 centimeter short axis.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 07 Feb 2023 (the median duration of follow-up was 56.61 months)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: months				
median (confidence interval 95%)	32.36 (23.129 to 40.016)	47.18 (38.965 to 57.922)		

Statistical analyses

Statistical analysis title	Statistical Analysis PFS2: Final Analysis 07Feb23

Statistical analysis description:

Analysis was performed on ITT population. Analysis was performed by Kaplan-Meier method.

Comparison groups	Carfilzomib + Dexamethasone (Kd) v Isatuximab + Carfilzomib + Dexamethasone (IKd)

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.663
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.491
upper limit	0.895

Notes:

[16] - Stratification was done on the number of prior lines of therapy (1 vs. >1) and R-ISS stage (I or II vs. III vs. not classified) according to IRT.

Secondary: HRQL: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 20 Items (EORTC QLQ-MY20): Disease Symptoms Domain Score at Specified Timepoints: Primary Analysis

End point title	HRQL: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 20 Items (EORTC QLQ-MY20): Disease Symptoms Domain Score at Specified Timepoints: Primary Analysis

End point description:

EORTC QLQ-MY20 is a validated questionnaire to assess the overall quality of life in subjects with multiple myeloma. It is used in conjunction with the EORTC QLQ-C30 to assess symptoms and side effects due to treatment or the disease. Disease symptoms domain is one of the four domain scores. Disease symptoms domain consist of 6 questions and the score uses 4-point scale (1 'Not at All' to 4 'Very Much'). Disease Symptoms Domain Score is calculated as ([{Q31+Q32+Q33+Q34+Q35+Q36}/6]-1)/3*100. Scores are averaged, and transformed to 0-100 scale, where higher scores = more symptoms and lower HRQL. Analysis was performed on ITT population. Here, 'n' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle (Cycle 2 to Cycle 25), at the End of Treatment visit (any day up to 114 weeks)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	123		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=103,157)	-5.34 (± 15.75)	-3.40 (± 19.58)		
Cycle 3 Day 1 (n=102, 158)	-8.28 (± 15.33)	-7.42 (± 18.15)		
Cycle 4 Day 1 (n=102, 152)	-5.45 (± 17.48)	-7.46 (± 17.99)		
Cycle 5 Day 1 (n=97, 150)	-5.78 (± 17.01)	-6.37 (± 18.32)		
Cycle 6 Day 1 (n=91, 146)	-6.11 (± 18.07)	-6.16 (± 19.88)		

Cycle 7 Day 1 (n=87, 143)	-6.64 (± 17.44)	-4.78 (± 20.77)		
Cycle 8 Day 1 (n=84, 136)	-6.94 (± 17.76)	-5.47 (± 19.96)		
Cycle 9 Day 1 (n=79, 131)	-5.65 (± 18.00)	-5.51 (± 17.86)		
Cycle 10 Day 1 (n=74, 125)	-5.56 (± 18.48)	-4.98 (± 17.24)		
Cycle 11 Day 1 (n=72, 122)	-3.24 (± 17.78)	-7.10 (± 17.57)		
Cycle 12 Day 1 (n=65, 121)	-5.30 (± 16.27)	-6.89 (± 17.58)		
Cycle 13 Day 1 (n=60, 114)	-7.69 (± 17.06)	-5.95 (± 16.44)		
Cycle 14 Day 1 (n=59, 113)	-8.66 (± 16.35)	-7.08 (± 17.98)		
Cycle 15 Day 1 (n=57, 105)	-5.56 (± 17.69)	-5.19 (± 17.84)		
Cycle 16 Day 1 (n=51, 102)	-8.06 (± 18.27)	-5.77 (± 18.66)		
Cycle 17 Day 1 (n=47, 101)	-7.57 (± 19.01)	-4.29 (± 19.73)		
Cycle 18 Day 1 (n=45, 94)	-7.16 (± 17.67)	-3.78 (± 17.93)		
Cycle 19 Day 1 (n=41, 90)	-7.18 (± 19.57)	-3.64 (± 16.70)		
Cycle 20 Day 1 (n=34, 88)	-11.93 (± 17.09)	-3.54 (± 21.63)		
Cycle 21 Day 1 (n=28, 73)	-9.72 (± 16.74)	-3.81 (± 19.70)		
Cycle 22 Day 1 (n=19, 54)	-9.94 (± 18.76)	-5.35 (± 22.48)		
Cycle 23 Day 1 (n=15, 37)	-5.56 (± 25.11)	-6.01 (± 19.53)		
Cycle 24 Day 1 (n=9, 22)	-6.17 (± 29.97)	-9.60 (± 18.16)		
Cycle 25 Day 1 (n=5, 16)	-12.22 (± 28.97)	-14.58 (± 21.65)		
End of Treatment (n=59, 57)	2.35 (± 23.10)	1.75 (± 23.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQL: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 20 Items (EORTC QLQ-MY20): Side Effects of Treatment at Specified Timepoints: Primary Analysis

End point title	HRQL: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 20 Items (EORTC QLQ-MY20): Side Effects of Treatment at Specified Timepoints: Primary Analysis

End point description:

EORTC QLQ-MY20 is a validated questionnaire to assess the overall quality of life in subjects with multiple myeloma. Side effects of treatment domain is one of the four domain scores. Side effects of treatment domain consists of 10 questions and the score uses a 4-point scale (1 'Not at All' to 4 'Very Much'). Side Effects of Treatment Score (MYSE) is calculated as ([{Q37+Q38+Q39+Q40+Q41+Q42+Q43+Q44+Q45+Q46}/10]-1)/3*100. Scores are averaged, and

transformed to 0-100 scale, where higher scores = more side effects and lower HRQL and lower scores = less side effects and better HRQL. Analysis was performed on ITT population. Here, 'n' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle (Cycle 2 to Cycle 25), at the End of Treatment visit (any day up to 114 weeks)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=103,157)	1.23 (± 11.56)	1.41 (± 11.71)		
Cycle 3 Day 1 (n=102, 158)	0.44 (± 10.11)	0.84 (± 12.00)		
Cycle 4 Day 1 (n=102, 152)	0.83 (± 11.38)	0.99 (± 11.89)		
Cycle 5 Day 1 (n=97, 150)	1.91 (± 11.36)	2.36 (± 11.94)		
Cycle 6 Day 1 (n=91, 146)	2.08 (± 11.81)	1.61 (± 12.32)		
Cycle 7 Day 1 (n=87, 143)	1.47 (± 12.14)	2.14 (± 10.76)		
Cycle 8 Day 1 (n=84, 136)	1.53 (± 12.07)	2.86 (± 12.77)		
Cycle 9 Day 1 (n=79, 131)	1.68 (± 11.57)	1.49 (± 11.96)		
Cycle 10 Day 1 (n=74, 125)	2.07 (± 11.62)	2.68 (± 12.51)		
Cycle 11 Day 1 (n=72, 122)	3.38 (± 12.00)	2.03 (± 12.16)		
Cycle 12 Day 1 (n=65, 121)	1.20 (± 10.52)	3.04 (± 12.72)		
Cycle 13 Day 1 (n=60, 114)	0.82 (± 10.22)	2.12 (± 12.33)		
Cycle 14 Day 1 (n=59, 113)	1.08 (± 10.56)	1.71 (± 12.58)		
Cycle 15 Day 1 (n=57, 105)	1.85 (± 11.45)	1.87 (± 11.80)		
Cycle 16 Day 1 (n=51, 102)	0.99 (± 10.54)	2.58 (± 11.88)		
Cycle 17 Day 1 (n=47, 101)	2.74 (± 10.03)	4.10 (± 12.77)		
Cycle 18 Day 1 (n=45, 94)	2.37 (± 10.51)	2.95 (± 13.38)		
Cycle 19 Day 1 (n=41, 90)	2.76 (± 11.41)	2.16 (± 11.56)		
Cycle 20 Day 1 (n=34, 88)	-0.17 (± 10.62)	2.05 (± 13.03)		
Cycle 21 Day 1 (n=28, 73)	3.17 (± 10.61)	2.74 (± 12.87)		
Cycle 22 Day 1 (n=19, 54)	3.55 (± 6.46)	1.51 (± 12.51)		
Cycle 23 Day 1 (n=15, 37)	7.85 (± 9.93)	-1.39 (± 12.02)		
Cycle 24 Day 1 (n=9, 22)	12.35 (± 7.17)	-2.54 (± 11.33)		
Cycle 25 Day 1 (n=5, 16)	11.85 (± 4.06)	-3.50 (± 12.83)		
End of Treatment (n=59, 57)	4.63 (± 13.01)	5.56 (± 16.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQL: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 20 Items (EORTC QLQ-MY20): Body Image Score at Specified Timepoints: Primary Analysis

End point title	HRQL: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 20 Items (EORTC QLQ-MY20): Body Image Score at Specified Timepoints: Primary Analysis

End point description:

EORTC QLQ-MY20 is a validated questionnaire to assess the overall quality of life in subjects with multiple myeloma. It is used in conjunction with the EORTC QLQ-C30 to assess symptoms and side effects due to treatment or the disease. It consists of one question and scores are based on the 4-point Likert scale ranging from 'Not at all' to 'Very much'. Body image score is calculated as: (1 – [Q47-1]/3)*100. Scores are averaged, and transformed to scale ranging from 0 to 100. A higher score represents a better quality of life. Analysis was performed on ITT population. Here, 'n' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle (Cycle 2 to Cycle 25), at the End of Treatment visit (any day up to 114 weeks)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=103,157)	-1.29 (± 23.76)	-1.27 (± 21.31)		
Cycle 3 Day 1 (n=101, 158)	1.98 (± 23.01)	1.27 (± 26.84)		
Cycle 4 Day 1 (n=101, 152)	-1.65 (± 25.55)	-1.10 (± 28.04)		
Cycle 5 Day 1 (n=97, 150)	-0.69 (± 26.34)	-2.89 (± 27.29)		
Cycle 6 Day 1 (n=91, 146)	-1.83 (± 24.02)	-1.60 (± 26.93)		
Cycle 7 Day 1 (n=87, 143)	-0.77 (± 27.83)	-3.03 (± 24.36)		
Cycle 8 Day 1 (n=84, 136)	-5.16 (± 25.08)	-0.25 (± 24.84)		
Cycle 9 Day 1 (n=78, 131)	-2.14 (± 24.82)	-1.02 (± 25.80)		
Cycle 10 Day 1 (n=74, 125)	-1.80 (± 25.22)	-1.33 (± 25.54)		
Cycle 11 Day 1 (n=72, 122)	-1.85 (± 29.01)	-0.55 (± 23.47)		
Cycle 12 Day 1 (n=65, 121)	-2.05 (± 25.60)	-0.55 (± 25.09)		
Cycle 13 Day 1 (n=60, 114)	-3.89 (± 26.10)	-2.63 (± 21.79)		
Cycle 14 Day 1 (n=59, 113)	-4.52 (± 26.59)	-3.24 (± 25.57)		
Cycle 15 Day 1 (n=57, 105)	0.00 (± 25.20)	-2.22 (± 24.58)		
Cycle 16 Day 1 (n=51, 102)	-1.31 (± 27.46)	-2.94 (± 22.55)		

Cycle 17 Day 1 (n=47, 101)	-1.42 (± 28.62)	-1.98 (± 26.17)		
Cycle 18 Day 1 (n=45, 94)	1.48 (± 30.11)	-1.77 (± 24.62)		
Cycle 19 Day 1 (n=41, 90)	0.00 (± 31.62)	-3.70 (± 26.18)		
Cycle 20 Day 1 (n=34, 88)	0.00 (± 27.22)	-0.76 (± 24.75)		
Cycle 21 Day 1 (n=28, 73)	-4.76 (± 34.80)	-3.20 (± 26.74)		
Cycle 22 Day 1 (n=19, 54)	-8.77 (± 36.59)	-1.85 (± 27.02)		
Cycle 23 Day 1 (n=15, 37)	-13.33 (± 30.34)	-5.41 (± 24.23)		
Cycle 24 Day 1 (n=9, 22)	-25.93 (± 36.43)	-3.03 (± 25.01)		
Cycle 25 Day 1 (n=5, 16)	-53.33 (± 18.26)	-8.33 (± 25.82)		
End of Treatment (n=59, 57)	-5.65 (± 21.58)	-9.36 (± 27.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQL: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 20 Items (EORTC QLQ-MY20): Future Perspective at Specified Timepoints: Primary Analysis

End point title	HRQL: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire With 20 Items (EORTC QLQ-MY20): Future Perspective at Specified Timepoints: Primary Analysis

End point description:

EORTC QLQ-MY20 is a validated questionnaire to assess the overall quality of life in subjects with multiple myeloma. It is used in conjunction with the EORTC QLQ-C30 to assess symptoms and side effects due to treatment or the disease. It consists of three questions and the scores are based on the 4-point Likert scale ranging from 'Not at all' to 'Very much'. Future Perspective score is calculated as (1 - ([{Q48+Q49+Q50}/3] -1)/3)*100. Scores are averaged and transformed to scale ranging from 0 to 100. A higher score represents a better quality of life. Analysis was performed on ITT population. Here, 'n' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle (Cycle 2 to Cycle 25), at the End of Treatment visit (any day up to 114 weeks)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=103,157)	0.54 (± 19.33)	7.57 (± 26.48)		

Cycle 3 Day 1 (n=101, 158)	4.84 (± 22.08)	9.70 (± 24.76)		
Cycle 4 Day 1 (n=101, 152)	6.60 (± 20.44)	8.55 (± 26.62)		
Cycle 5 Day 1 (n=97, 150)	7.67 (± 22.64)	7.56 (± 26.98)		
Cycle 6 Day 1 (n=91, 146)	8.42 (± 21.81)	9.97 (± 25.70)		
Cycle 7 Day 1 (n=87, 143)	8.17 (± 21.93)	8.47 (± 24.74)		
Cycle 8 Day 1 (n=84, 136)	7.41 (± 22.51)	10.54 (± 24.50)		
Cycle 9 Day 1 (n=78, 131)	7.26 (± 21.10)	8.57 (± 28.26)		
Cycle 10 Day 1 (n=74, 125)	8.56 (± 22.79)	11.56 (± 24.82)		
Cycle 11 Day 1 (n=72, 122)	8.02 (± 21.69)	12.02 (± 24.23)		
Cycle 12 Day 1 (n=65, 121)	6.84 (± 24.51)	11.48 (± 22.90)		
Cycle 13 Day 1 (n=60, 114)	11.11 (± 20.04)	10.72 (± 23.18)		
Cycle 14 Day 1 (n=59, 113)	8.85 (± 22.86)	11.31 (± 23.29)		
Cycle 15 Day 1 (n=57, 105)	9.55 (± 24.16)	12.28 (± 22.27)		
Cycle 16 Day 1 (n=51, 102)	12.42 (± 24.51)	11.76 (± 25.20)		
Cycle 17 Day 1 (n=47, 101)	12.29 (± 21.64)	10.89 (± 25.29)		
Cycle 18 Day 1 (n=45, 94)	11.36 (± 22.41)	7.33 (± 23.25)		
Cycle 19 Day 1 (n=41, 90)	9.21 (± 24.96)	8.40 (± 25.50)		
Cycle 20 Day 1 (n=34, 88)	10.13 (± 24.67)	9.60 (± 25.34)		
Cycle 21 Day 1 (n=28, 73)	10.32 (± 22.41)	10.65 (± 26.15)		
Cycle 22 Day 1 (n=19, 54)	8.77 (± 25.28)	12.14 (± 22.35)		
Cycle 23 Day 1 (n=15, 37)	9.63 (± 27.81)	12.61 (± 20.48)		
Cycle 24 Day 1 (n=9, 22)	1.23 (± 24.50)	16.16 (± 18.70)		
Cycle 25 Day 1 (n=5, 16)	-4.44 (± 24.34)	15.28 (± 16.67)		
End of Treatment (n=59, 57)	-3.95 (± 22.86)	-3.70 (± 31.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQL: Change from Baseline in European Quality of Life Group Questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L): Health State Utility Index Value at Specified Timepoints: Primary Analysis

End point title	HRQL: Change from Baseline in European Quality of Life Group Questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L): Health State Utility Index Value at Specified Timepoints: Primary Analysis

End point description:

The EQ-5D-5L is a standardized measure of health status that provides a general assessment of health utility and consist in 2 sections a descriptive system comprising 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and Visual Analog Scale (VAS). Each dimension has a

5-level response: no problems, slight problems, moderate problems, severe problems, and extreme problems. Response options are measured with a 5-point Likert scale. The 5D-5L systems are converted into a single index utility score between 0 to 1, where higher score indicates a better health state and lower score indicate worse health state. Analysis was performed on ITT population. Here, 'n' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle (Cycle 2 to Cycle 25), at the End of Treatment visit (any day up to 114 weeks)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=99,151)	0.05 (± 0.17)	0.04 (± 0.19)		
Cycle 3 Day 1 (n=98, 150)	0.06 (± 0.21)	0.05 (± 0.22)		
Cycle 4 Day 1 (n=99, 147)	0.02 (± 0.21)	0.05 (± 0.21)		
Cycle 5 Day 1 (n=95, 144)	0.04 (± 0.20)	0.04 (± 0.20)		
Cycle 6 Day 1 (n=88, 141)	0.03 (± 0.19)	0.05 (± 0.23)		
Cycle 7 Day 1 (n=85, 139)	0.06 (± 0.19)	0.04 (± 0.21)		
Cycle 8 Day 1 (n=81, 132)	0.06 (± 0.19)	0.05 (± 0.22)		
Cycle 9 Day 1 (n=77, 124)	0.05 (± 0.20)	0.04 (± 0.19)		
Cycle 10 Day 1 (n=71, 120)	0.06 (± 0.22)	0.03 (± 0.22)		
Cycle 11 Day 1 (n=69, 118)	0.04 (± 0.23)	0.05 (± 0.20)		
Cycle 12 Day 1 (n=63, 115)	0.03 (± 0.16)	0.02 (± 0.20)		
Cycle 13 Day 1 (n=59, 109)	0.06 (± 0.16)	0.03 (± 0.19)		
Cycle 14 Day 1 (n=58, 109)	0.06 (± 0.24)	0.04 (± 0.19)		
Cycle 15 Day 1 (n=57, 101)	0.05 (± 0.18)	0.05 (± 0.18)		
Cycle 16 Day 1 (n=50, 98)	0.06 (± 0.16)	0.04 (± 0.19)		
Cycle 17 Day 1 (n=46, 97)	0.05 (± 0.15)	0.03 (± 0.20)		
Cycle 18 Day 1 (n=45, 90)	0.02 (± 0.15)	0.04 (± 0.17)		
Cycle 19 Day 1 (n=41, 86)	0.03 (± 0.20)	0.03 (± 0.18)		
Cycle 20 Day 1 (n=34, 85)	0.06 (± 0.17)	0.03 (± 0.23)		
Cycle 21 Day 1 (n=28, 70)	0.03 (± 0.15)	0.02 (± 0.22)		
Cycle 22 Day 1 (n=19, 52)	0.05 (± 0.19)	0.02 (± 0.22)		
Cycle 23 Day 1 (n=15, 36)	0.05 (± 0.18)	0.00 (± 0.27)		
Cycle 24 Day 1 (n=9, 22)	0.04 (± 0.24)	0.03 (± 0.20)		
Cycle 25 Day 1 (n=5, 16)	0.05 (± 0.38)	0.04 (± 0.22)		
End of Treatment (n=57, 56)	-0.03 (± 0.25)	-0.08 (± 0.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQL: Change From Baseline in European Quality of Life Working Group

Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Score: Visual Analogic Scale (VAS) at Specified Timepoints: Primary Analysis

End point title	HRQL: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Score: Visual Analogic Scale (VAS) at Specified Timepoints: Primary Analysis

End point description:

The EQ-5D-5L is a standardised measure of health status that provides a general assessment of health utility and consist of 2 sections; descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS. The VAS records the respondent's self-rated health on a 20 centimeter (cm) vertical VAS; the scale went from 0 (worst imaginable health state) to 100 (best imaginable health state). This information can be used as a quantitative measure of health as judged by the individual respondents. Analysis was performed on ITT population. Here, 'n' signifies subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle (Cycle 2 to Cycle 25), at the End of Treatment visit (any day up to 114 weeks)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	179		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=99,151)	2.42 (± 17.04)	0.60 (± 15.23)		
Cycle 3 Day 1 (n=98, 150)	4.70 (± 16.13)	3.47 (± 17.80)		
Cycle 4 Day 1 (n=99, 147)	6.03 (± 16.73)	2.29 (± 18.69)		
Cycle 5 Day 1 (n=94, 144)	3.40 (± 16.89)	2.35 (± 19.73)		
Cycle 6 Day 1 (n=88, 141)	2.80 (± 18.56)	1.24 (± 19.11)		
Cycle 7 Day 1 (n=84, 139)	0.64 (± 21.69)	2.24 (± 18.85)		
Cycle 8 Day 1 (n=81, 132)	1.48 (± 17.11)	2.40 (± 18.87)		
Cycle 9 Day 1 (n=77, 124)	-0.14 (± 17.46)	2.93 (± 19.04)		
Cycle 10 Day 1 (n=71, 120)	2.76 (± 17.41)	2.82 (± 18.35)		
Cycle 11 Day 1 (n=69, 118)	3.86 (± 20.07)	3.77 (± 18.51)		
Cycle 12 Day 1 (n=63, 115)	5.29 (± 18.51)	3.63 (± 19.34)		
Cycle 13 Day 1 (n=59, 109)	6.81 (± 19.57)	4.94 (± 18.41)		
Cycle 14 Day 1 (n=58, 109)	7.95 (± 18.12)	4.72 (± 4.72)		
Cycle 15 Day 1 (n=57, 101)	4.96 (± 18.92)	3.23 (± 18.87)		
Cycle 16 Day 1 (n=50, 98)	3.94 (± 18.78)	4.56 (± 18.88)		
Cycle 17 Day 1 (n=46, 97)	5.04 (± 17.93)	4.97 (± 18.55)		
Cycle 18 Day 1 (n=45, 90)	3.71 (± 19.08)	3.83 (± 18.46)		
Cycle 19 Day 1 (n=41, 86)	7.44 (± 18.73)	3.69 (± 18.37)		
Cycle 20 Day 1 (n=34, 85)	6.18 (± 18.43)	4.20 (± 17.20)		
Cycle 21 Day 1 (n=28, 70)	7.25 (± 23.46)	3.26 (± 18.97)		
Cycle 22 Day 1 (n=19, 52)	5.58 (± 24.06)	2.35 (± 18.62)		
Cycle 23 Day 1 (n=15, 36)	6.33 (± 18.73)	6.44 (± 18.34)		
Cycle 24 Day 1 (n=9, 22)	5.11 (± 17.93)	4.50 (± 18.31)		
Cycle 25 Day 1 (n=5, 16)	9.20 (± 21.48)	5.00 (± 18.83)		

End of Treatment (n=57, 56)	-4.40 (± 18.66)	-7.80 (± 21.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Plasma Concentration at End of infusion (Ceoi) of Isatuximab: Primary Analysis

End point title	Pharmacokinetics: Plasma Concentration at End of infusion (Ceoi) of Isatuximab: Primary Analysis[17]

End point description:

Ceoi is the plasma concentration observed at the end of intravenous infusion. Analysis was performed on pharmacokinetic (PK) population which included subjects who received at least 1 dose of Isatuximab, with data for at least 1 PK parameter available. Here, 'n' signifies number of subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

End of infusion on Cycle 1 Day 1 and Cycle 1 Day 15; Cycle 2 Day 1

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: microgram/milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=169)	274.01 (± 183.67)			
Cycle 1 Day 15 (n=27)	380.28 (± 85.70)			
Cycle 2 Day 1 (n=161)	522.74 (± 204.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Plasma concentration of Isatuximab at Ctrough: Primary Analysis

End point title	Pharmacokinetics: Plasma concentration of Isatuximab at Ctrough: Primary Analysis[18]

End point description:

Ctrough was the plasma concentration observed just before treatment administration during repeated

dosing. Analysis was performed on PK population. Here, 'n' signifies number of subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Pre-infusion on Cycle 1 Day 1, Day 8, Day 15 and Day 22, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 7 Day 1, Cycle 8 Day 1, Cycle 9 Day 1 and Cycle 10 Day 1

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=166)	3.66 (± 34.40)			
Cycle 1 Day 8 (n=152)	82.14 (± 43.87)			
Cycle 1 Day 15 (n=144)	180.02 (± 71.83)			
Cycle 1 Day 22 (n=147)	252.63 (± 100.16)			
Cycle 2 Day 1 (n=130)	324.28 (± 132.98)			
Cycle 3 Day 1 (n=145)	295.78 (± 146.11)			
Cycle 4 Day 1 (n=137)	342.48 (± 140.94)			
Cycle 5 Day 1 (n=135)	389.25 (± 172.11)			
Cycle 6 Day 1 (n=130)	427.16 (± 188.51)			
Cycle 7 Day 1 (n=123)	433.22 (± 177.11)			
Cycle 8 Day 1 (n=118)	490.51 (± 198.17)			
Cycle 9 Day 1 (n=113)	486.07 (± 181.34)			
Cycle 10 Day 1 (n=100)	490.08 (± 206.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Maximum Observed Concentration (Cmax) of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: Maximum Observed Concentration (Cmax) of Carfilzomib: Primary Analysis[19]

End point description:

Cmax was defined as the maximum concentration observed after the first infusion calculated using the

non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 minutes (min), 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)	2090 (± 1360)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Clast of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: Clast of Carfilzomib: Primary Analysis[20]

End point description:

Clast was defined as the last concentration observed above the lower limit of quantification. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ng/mL				
arithmetic mean (standard deviation)	3.00 (± 5.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Volume of Distribution at Steady State (Vss) of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: Volume of Distribution at Steady State (Vss) of Carfilzomib: Primary Analysis[21]

End point description:

Volume of Distribution was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Vss is the apparent volume of distribution at steady-state, calculated using the non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: liters				
arithmetic mean (standard deviation)	453 (± 1570)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Area under the Plasma concentration time curve from time 0 to last quantifiable concentration (AUClast) of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: Area under the Plasma concentration time curve from time 0 to last quantifiable concentration (AUClast) of Carfilzomib: Primary Analysis[22]

End point description:

AUClast was defined as area under the plasma concentration versus time curve calculated from time 0 to last quantifiable concentration. AUClast was calculated using the non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ng*h/mL				
arithmetic mean (standard deviation)	779 (± 505)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Area Under the Plasma Concentration Time Curve (AUC) of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: Area Under the Plasma Concentration Time Curve (AUC) of Carfilzomib: Primary Analysis[23]

End point description:

AUC was defined as area under the plasma concentration-time curve extrapolated to infinity according to the equation: AUC= AUClast + Clast/λz. AUC was calculated using the non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: nanograms*hour/milliliter(ng*h/mL)				
arithmetic mean (standard deviation)	784 (± 509)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: tlast of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: tlast of Carfilzomib: Primary Analysis[24]

End point description:

Tlast was defined as the time of last concentration observed above the lower limit of quantification, calculated using the non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (full range (min-max))	4.50 (2.52 to 4.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Terminal Half-life (t1/2z) of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: Terminal Half-life (t1/2z) of Carfilzomib: Primary Analysis[25]

End point description:

T1/2 was defined as the time required for the concentration of the drug to reach half of its original value, calculated using the non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (full range (min-max))	0.860 (0.450 to 1.89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Clearance at Steady State (CLss) of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: Clearance at Steady State (CLss) of Carfilzomib: Primary Analysis[26]

End point description:

CLss was defined as a quantitative measure of the rate at which a drug substance is removed from the body at steady state, calculated using the non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Liters/hour (L/h)				
arithmetic mean (standard deviation)	466 (± 1190)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: tmax of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: tmax of Carfilzomib: Primary Analysis[27]

End point description:

Tmax was defined as the time to reach Cmax, calculated using the non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (full range (min-max))	0.54 (0.35 to 0.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Percentage of extrapolation of AUC (AUCext) of Carfilzomib: Primary Analysis

End point title	Pharmacokinetics: Percentage of extrapolation of AUC (AUCext) of Carfilzomib: Primary Analysis[28]

End point description:

AUCext was defined as the percentage of the extrapolation of AUC, calculated using the non-compartmental analysis after the intravenous infusion of carfilzomib with isatuximab. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1: pre-dose (0 hour), 30 min, 35 min, 45 min, 60 min, 1 hour 30 min, 2 hours 30 min and 4 hours 30 min post-dose on Day 15

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percentage of AUC				
geometric mean (geometric coefficient of variation)	0 (± 172)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs): LPLV Analysis

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs): LPLV Analysis

End point description:

Adverse Event (AE) was defined as any untoward medical occurrence in a subject who received study drug and did not necessarily had a causal relationship with the treatment. TEAEs were defined as AEs that developed, worsened, or became serious during the treatment period (time from the first dose of study treatments up to 30 days after last dose of study treatments). An SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalization, resulted in persistent or significant disability / incapacity, was a congenital anomaly/birth defect, was a medically important event. Analysis was performed on safety population which included all subjects who gave their informed consent and for whom there was confirmation of successful allocation of a randomisation number by the IRT and received at least one dose or a part of a dose of the study treatments.

End point type	Secondary

End point timeframe:

From first dose of study treatment administration (Day 1) up to 30 days post last dose of study treatment administration, up to 349 weeks for Kd arm and 356 weeks for IKd arm (maximum duration of treatment exposure)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	177		
Units: subjects				
Any TEAE	119	175		
Any treatment emergent SAE	74	129		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Anti-Drug Antibodies (ADA): Primary Analysis

End point title	Number of Subjects with Anti-Drug Antibodies (ADA): Primary Analysis[29]

End point description:

ADA were categorised as: pre-existing, treatment induced, and treatment boosted response. Pre-existing ADA was defined as ADA that were present in samples drawn during the pretreatment period (i.

e., before the first isatuximab administration). Treatment-induced ADA was defined as ADA that developed at any time during the ADA on-study observation period in subjects without pre-existing ADA, including subjects without pretreatment samples. Treatment boosted ADA was defined as pre-existing ADA with an increase in titer during the ADA on-study observation period. Analysis was performed on ADA evaluable population which included subjects who received at least one dose of study drug from the IKd arm with at least one ADA assessment during the ADA on-study observation period with a reportable result.

End point type	Secondary

End point timeframe:

From first dose of study treatment up to 30 days after last dose of study treatment (maximum duration: 111 weeks)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analysed for Kd arm.

End point values	Isatuximab + Carfilzomib + Dexamethasone (IKd)			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: subjects				
Pre-existing ADA	0			
Treatment induced ADA	0			
Treatment boosted ADA	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Renal Response (RR): Primary Analysis

End point title	Number of Subjects with Renal Response (RR): Primary Analysis

End point description:

RR comprises of complete RR (CR renal), partial RR (PR renal) & minor RR (MR renal). CR renal: improvement in estimated glomerular filtration rate (eGFR) from <50 mL/min/1.73m^2 at Baseline to >=60 mL/min/1.73m^2 in at least 1 assessment during treatment period (time from 1st dose of study treatment [ST] up to 30 days after last dose of ST); PR renal: improvement in eGFR from <15 mL/min/1.73m^2 at baseline to at least 1 assessment in range of 30 to 60 mL/min/1.73m^2 during on treatment-period (OTP) & MR renal: improvement in eGFR from <15 mL/min/1.73m^2 at baseline to at least 1 assessment in range of 15-30 mL/min/1.73m^2 during OTP/from 15-30 mL/min/1.73m^2 at Baseline to at least 1 assessment in range of 30 to 60 mL/min/1.73m^2 during OTP. Analysis on ITT population. 'Number of subjects analysed' = subjects with available data for the endpoint & 'n' = subjects with available data for each category. 99999 signifies no subjects available for assessment at specified timepoint.

End point type	Secondary

End point timeframe:

From the first dose of study treatment to 30 days following the last administration of study treatment (maximum duration: up to 114 weeks)

End point values	Carfilzomib + Dexamethasone (Kd)	Isatuximab + Carfilzomib + Dexamethasone (IKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: number of subjects				
CR Renal (n=13,25)	4	13		
PR Renal (n=0,0)	99999	99999		
MR Renal (n=3,4)	1	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data was collected from first dose of study treatment administration (Day 1) up to 30 days post last dose of study treatment administration, up to 349 weeks for Kd arm and 356 weeks for IKd arm (maximum duration of treatment exposure).

Adverse event reporting additional description:

Data was collected in safety population that included participants who received at least 1 dose or a part of a dose of the study treatments. Reported AEs, SAEs, & deaths are TEAEs that developed, worsened or became serious during the treatment period (from the 1st dose of study treatments up to 30 days after last dose of study treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Isatuximab + Carfilzomib + Dexamethasone (IKd)
Reporting group description: -	
Reporting group title	Carfilzomib + Dexamethasone (Kd)

Reporting group description: -

Serious adverse events	Isatuximab + Carfilzomib + Dexamethasone (IKd)	Carfilzomib + Dexamethasone (Kd)	
Total subjects affected by serious adverse events			
subjects affected / exposed	129 / 177 (72.88%)	74 / 122 (60.66%)	
number of deaths (all causes)	82	59	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal Squamous Cell Carcinoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Squamous Cell Carcinoma Stage Ii			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			

subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's Disease			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer Female			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon Cancer			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal Cancer Stage I			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Cell Lung Cancer			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm Malignant			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Second Primary Malignancy			

subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Cancer			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Plasma Cell Leukaemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse Large B-Cell Lymphoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leptomeningeal Myelomatosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Extremity Necrosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			
subjects affected / exposed	3 / 177 (1.69%)	4 / 122 (3.28%)	
occurrences causally related to treatment / all	1 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous Thrombosis Limb			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Peripheral Swelling			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection Site Extravasation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease Progression			
subjects affected / exposed	1 / 177 (0.56%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Death			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	4 / 177 (2.26%)	3 / 122 (2.46%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 177 (0.00%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Paraphimosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	2 / 177 (1.13%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Hypertension			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	3 / 177 (1.69%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Product issues			
Device Malfunction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Plasma Cells Increased			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grip Strength Decreased			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T Wave Inversion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Marrow Plasmacyte Count Increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatinine Increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 177 (2.26%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			

subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Contusion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia Postoperative			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Related Reaction			
subjects affected / exposed	3 / 177 (1.69%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Injury			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Traumatic Fracture			
subjects affected / exposed	5 / 177 (2.82%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Injuries			

subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Craniofacial Fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Subarachnoid Haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left Ventricular Failure			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Coronary Syndrome			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	1 / 177 (0.56%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina Pectoris			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Valve Stenosis			

subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	3 / 177 (1.69%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Stenosis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Insufficiency			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis Coronary Artery			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			

subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	5 / 177 (2.82%)	4 / 122 (3.28%)	
occurrences causally related to treatment / all	1 / 6	4 / 5	
deaths causally related to treatment / all	0 / 2	1 / 1	
Cardiac Hypertrophy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral Nerve Paresis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 177 (0.56%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial Mass			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic Cerebral Infarction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid Artery Stenosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normocytic Anaemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			

subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness Neurosensory			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Large Intestine Perforation			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 177 (1.13%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ischaemic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal Perforation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug Eruption			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Foot			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal Colic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic Syndrome			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Calculus Urinary			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Kidney Injury			
subjects affected / exposed	3 / 177 (1.69%)	5 / 122 (4.10%)	
occurrences causally related to treatment / all	1 / 3	4 / 7	
deaths causally related to treatment / all	0 / 1	1 / 1	
Musculoskeletal and connective tissue disorders			
Pain In Extremity			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	3 / 177 (1.69%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis Of Jaw			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	5 / 177 (2.82%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sympathetic Posterior Cervical Syndrome			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid Arthritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Wall Haematoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Abdominal Abscess			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Sepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical Pneumonia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bacterial Sepsis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 177 (1.69%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Pneumococcal			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			

subjects affected / exposed	5 / 177 (2.82%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Covid-19 Pneumonia			
subjects affected / exposed	4 / 177 (2.26%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Campylobacter Gastroenteritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 177 (1.69%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus Viraemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Bacteraemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae Virus Infection			
subjects affected / exposed	2 / 177 (1.13%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 177 (1.13%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Salmonella			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 Influenza			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H3n2 Influenza			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma Infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	2 / 177 (1.13%)	5 / 122 (4.10%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	8 / 177 (4.52%)	6 / 122 (4.92%)	
occurrences causally related to treatment / all	2 / 8	3 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus Pneumonia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Respiratory Syncytial Viral			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis Infective			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis Jirovecii Pneumonia			

subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	41 / 177 (23.16%)	17 / 122 (13.93%)	
occurrences causally related to treatment / all	15 / 54	8 / 20	
deaths causally related to treatment / all	0 / 5	0 / 1	
Pneumonia Influenzal			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Legionella			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Pyelonephritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 177 (3.39%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	2 / 177 (1.13%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Bacterial			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Device Infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 177 (1.69%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visceral Leishmaniasis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy Bacterial			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Streptococcal			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Viral			
subjects affected / exposed	2 / 177 (1.13%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Sepsis			

subjects affected / exposed	2 / 177 (1.13%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Syncytial Virus Bronchitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Syncytial Virus Infection			
subjects affected / exposed	3 / 177 (1.69%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	4 / 177 (2.26%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 177 (2.26%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			

subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal Sepsis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Mineral Metabolism Disorder			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Lysis Syndrome			
subjects affected / exposed	0 / 177 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus			
subjects affected / exposed	1 / 177 (0.56%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	3 / 177 (1.69%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	2 / 177 (1.13%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Isatuximab + Carfilzomib + Dexamethasone (IKd)	Carfilzomib + Dexamethasone (Kd)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 177 (94.35%)	113 / 122 (92.62%)	
Vascular disorders			
Superficial Vein Thrombosis			
subjects affected / exposed	10 / 177 (5.65%)	7 / 122 (5.74%)	
occurrences (all)	13	12	
Deep Vein Thrombosis			
subjects affected / exposed	8 / 177 (4.52%)	8 / 122 (6.56%)	
occurrences (all)	12	9	
Hypertension			
subjects affected / exposed	69 / 177 (38.98%)	42 / 122 (34.43%)	
occurrences (all)	109	66	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	36 / 177 (20.34%)	21 / 122 (17.21%)	
occurrences (all)	71	30	
Fatigue			
subjects affected / exposed	57 / 177 (32.20%)	25 / 122 (20.49%)	
occurrences (all)	82	29	
Oedema Peripheral			
subjects affected / exposed	30 / 177 (16.95%)	21 / 122 (17.21%)	
occurrences (all)	48	31	
Non-Cardiac Chest Pain			
subjects affected / exposed	11 / 177 (6.21%)	7 / 122 (5.74%)	
occurrences (all)	11	8	
Influenza Like Illness			

subjects affected / exposed	9 / 177 (5.08%)	5 / 122 (4.10%)	
occurrences (all)	13	9	
Pyrexia			
subjects affected / exposed	22 / 177 (12.43%)	21 / 122 (17.21%)	
occurrences (all)	34	31	
Respiratory, thoracic and mediastinal disorders			
Productive Cough			
subjects affected / exposed	10 / 177 (5.65%)	2 / 122 (1.64%)	
occurrences (all)	13	2	
Cough			
subjects affected / exposed	41 / 177 (23.16%)	18 / 122 (14.75%)	
occurrences (all)	64	30	
Dyspnoea			
subjects affected / exposed	54 / 177 (30.51%)	28 / 122 (22.95%)	
occurrences (all)	76	42	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	46 / 177 (25.99%)	30 / 122 (24.59%)	
occurrences (all)	54	43	
Anxiety			
subjects affected / exposed	15 / 177 (8.47%)	4 / 122 (3.28%)	
occurrences (all)	18	5	
Investigations			
Weight Decreased			
subjects affected / exposed	13 / 177 (7.34%)	1 / 122 (0.82%)	
occurrences (all)	13	1	
Injury, poisoning and procedural complications			
Skin Laceration			
subjects affected / exposed	11 / 177 (6.21%)	3 / 122 (2.46%)	
occurrences (all)	34	7	
Traumatic Fracture			
subjects affected / exposed	12 / 177 (6.78%)	4 / 122 (3.28%)	
occurrences (all)	13	5	
Contusion			
subjects affected / exposed	12 / 177 (6.78%)	6 / 122 (4.92%)	
occurrences (all)	19	13	

Accidental Overdose			
subjects affected / exposed	17 / 177 (9.60%)	7 / 122 (5.74%)	
occurrences (all)	41	8	
Limb Injury			
subjects affected / exposed	11 / 177 (6.21%)	3 / 122 (2.46%)	
occurrences (all)	12	5	
Fall			
subjects affected / exposed	23 / 177 (12.99%)	12 / 122 (9.84%)	
occurrences (all)	31	23	
Infusion Related Reaction			
subjects affected / exposed	80 / 177 (45.20%)	4 / 122 (3.28%)	
occurrences (all)	122	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 177 (5.08%)	7 / 122 (5.74%)	
occurrences (all)	13	11	
Headache			
subjects affected / exposed	30 / 177 (16.95%)	22 / 122 (18.03%)	
occurrences (all)	43	41	
Peripheral Sensory Neuropathy			
subjects affected / exposed	30 / 177 (16.95%)	16 / 122 (13.11%)	
occurrences (all)	36	24	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	11 / 177 (6.21%)	1 / 122 (0.82%)	
occurrences (all)	20	1	
Thrombocytopenia			
subjects affected / exposed	6 / 177 (3.39%)	11 / 122 (9.02%)	
occurrences (all)	6	13	
Anaemia			
subjects affected / exposed	9 / 177 (5.08%)	5 / 122 (4.10%)	
occurrences (all)	9	5	
Eye disorders			
Cataract			
subjects affected / exposed	31 / 177 (17.51%)	12 / 122 (9.84%)	
occurrences (all)	37	13	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	25 / 177 (14.12%)	13 / 122 (10.66%)	
occurrences (all)	33	17	
Diarrhoea			
subjects affected / exposed	72 / 177 (40.68%)	38 / 122 (31.15%)	
occurrences (all)	134	55	
Abdominal Pain			
subjects affected / exposed	8 / 177 (4.52%)	9 / 122 (7.38%)	
occurrences (all)	12	10	
Dyspepsia			
subjects affected / exposed	17 / 177 (9.60%)	5 / 122 (4.10%)	
occurrences (all)	25	5	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	12 / 177 (6.78%)	5 / 122 (4.10%)	
occurrences (all)	12	5	
Nausea			
subjects affected / exposed	39 / 177 (22.03%)	22 / 122 (18.03%)	
occurrences (all)	95	35	
Vomiting			
subjects affected / exposed	29 / 177 (16.38%)	13 / 122 (10.66%)	
occurrences (all)	49	25	
Abdominal Pain Upper			
subjects affected / exposed	9 / 177 (5.08%)	5 / 122 (4.10%)	
occurrences (all)	12	5	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	9 / 177 (5.08%)	2 / 122 (1.64%)	
occurrences (all)	12	2	
Rash			
subjects affected / exposed	13 / 177 (7.34%)	9 / 122 (7.38%)	
occurrences (all)	15	10	
Musculoskeletal and connective tissue disorders			
Muscular Weakness			
subjects affected / exposed	6 / 177 (3.39%)	11 / 122 (9.02%)	
occurrences (all)	8	14	
Muscle Spasms			

subjects affected / exposed	28 / 177 (15.82%)	19 / 122 (15.57%)	
occurrences (all)	41	26	
Bone Pain			
subjects affected / exposed	14 / 177 (7.91%)	9 / 122 (7.38%)	
occurrences (all)	18	12	
Back Pain			
subjects affected / exposed	43 / 177 (24.29%)	25 / 122 (20.49%)	
occurrences (all)	60	34	
Musculoskeletal Chest Pain			
subjects affected / exposed	9 / 177 (5.08%)	8 / 122 (6.56%)	
occurrences (all)	9	9	
Arthralgia			
subjects affected / exposed	41 / 177 (23.16%)	14 / 122 (11.48%)	
occurrences (all)	64	20	
Myalgia			
subjects affected / exposed	12 / 177 (6.78%)	6 / 122 (4.92%)	
occurrences (all)	12	7	
Pain In Extremity			
subjects affected / exposed	27 / 177 (15.25%)	17 / 122 (13.93%)	
occurrences (all)	36	20	
Infections and infestations			
Influenza			
subjects affected / exposed	20 / 177 (11.30%)	13 / 122 (10.66%)	
occurrences (all)	27	26	
Respiratory Tract Infection			
subjects affected / exposed	19 / 177 (10.73%)	7 / 122 (5.74%)	
occurrences (all)	49	10	
Rhinitis			
subjects affected / exposed	11 / 177 (6.21%)	3 / 122 (2.46%)	
occurrences (all)	18	4	
Sinusitis			
subjects affected / exposed	12 / 177 (6.78%)	5 / 122 (4.10%)	
occurrences (all)	20	8	
Upper Respiratory Tract Infection			
subjects affected / exposed	73 / 177 (41.24%)	32 / 122 (26.23%)	
occurrences (all)	189	51	

Urinary Tract Infection			
subjects affected / exposed	19 / 177 (10.73%)	11 / 122 (9.02%)	
occurrences (all)	32	21	
Pneumonia			
subjects affected / exposed	18 / 177 (10.17%)	13 / 122 (10.66%)	
occurrences (all)	21	21	
Nasopharyngitis			
subjects affected / exposed	36 / 177 (20.34%)	16 / 122 (13.11%)	
occurrences (all)	51	30	
Bronchitis			
subjects affected / exposed	43 / 177 (24.29%)	14 / 122 (11.48%)	
occurrences (all)	71	22	
Covid-19			
subjects affected / exposed	26 / 177 (14.69%)	2 / 122 (1.64%)	
occurrences (all)	31	2	
Conjunctivitis			
subjects affected / exposed	12 / 177 (6.78%)	9 / 122 (7.38%)	
occurrences (all)	13	13	
Gastroenteritis			
subjects affected / exposed	19 / 177 (10.73%)	7 / 122 (5.74%)	
occurrences (all)	23	7	
Lower Respiratory Tract Infection			
subjects affected / exposed	12 / 177 (6.78%)	8 / 122 (6.56%)	
occurrences (all)	16	12	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	14 / 177 (7.91%)	5 / 122 (4.10%)	
occurrences (all)	18	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2017	Infusion time of carfilzomib changed from 10 to 30 minutes to be consistent with SMPC/PI.
08 February 2018	Added objective to evaluate rate of VGPR/better in subjects who were MRD negative, Removed local laboratory testing for response to reduce number of blood samples drawn, Added Coombs test after treatment was initiated to assess assay interference, Changed frequency of pregnancy testing & added appendix with additional pregnancy testing requirements, Allowed urine pregnancy test. Added Grade 5 IARs & symptomatic NIMP overdose as AESIs, HR estimate & corresponding 95% CI was changed to HR & corresponding (1-2α)% (α: 1-sided nominal significance level: α=0.023 at final analysis & 0.005 at PFS interim analysis), Added serologic definition of active hepatitis B & C, Clarified instructions for duration of contraceptive measures, Clarified that further anti myeloma therapies be collected until OS analysis, Clarified that hydration prior carfilzomib could be <500 mL (but >250 mL) during 2 first infusions for subjects at risk of cardiac decompensation, G-CSF use no longer limited to 1st 3 cycles, Added treatment delays for subject convenience be avoided during 1st cycles, Modified recommended actions for low ANC & platelet count, Added delay for carfilzomib infusion if Grade 3-4 IR occurred during isatuximab infusion, Added Appendix with description of low dose body CT scan, Added PFS2 be assessed by Investigator, Added when confirmatory disease assessments be repeated at 3 month intervals, Added subjects with history of hypertension had to have controlled BP before dosing, Added hydration requirements predose if TLS observed at prior infusion.
02 July 2018	BMA is an invasive procedure and study allows up to 6 BMAs. To limit the number of BMAs, wording to trigger BMA was clarified, In absence of radiological and M protein progression, if clinical and biological data together provided clear evidence of clinical progression based on IRC judgement, the IRC could consider clinical progression as a PFS event, Czech Republic added to appendix list of countries with increased pregnancy testing, For exclusion criterion 12: Clarified that only curative radiotherapy was allowed within 14 days prior to randomization, Clarified that any therapy (not just chemotherapy) for other cancer should have been completed at least 5 years prior to enrollment, Allowed oral diphenhydramine or equivalent in country where there is no longer IV formulation, Added possibility of keeping the same hydration volume and lengthening the administration time in case of cardiac decompensation risk, Clarified rules for dose modifications, Added protocol recommendations regarding antibacterial prophylaxis and thromboprophylaxis, and added caution regarding cotreatment of dexamethasone with CYP3A inhibitor.
11 June 2019	Contraception duration after end of isatuximab changed from 3 months (12 weeks) to 5 months, Change in frequency of pregnancy test per country requirement for women with childbearing potential; pregnancy test was to be performed before each cycle and then monthly during the follow-up period up to 3 months (12 weeks) in the Kd arm and up to 5 months in the IKd arm.
11 September 2019	Implemented safety monitoring measures following identification of 2 new risks related to carfilzomib - Carfilzomib may increase risk of progressive multifocal leukoencephalopathy & Carfilzomib may increase risk of hepatitis B virus reactivation.

13 November 2019	Based on Health Authority feedback, censoring rules for the primary PFS analysis were changed; PFS2 was also updated according to the change. Hepatitis B virus DNA testing by polymerase chain reaction was added for patients with a positive hepatitis B surface antigen test and/or anti-Hepatitis B core antibody test, Added that any second primary malignancies during the follow-up period will be reported, Statistical sections were updated to match Statistical Analysis Plan amendment of July 2019 and changes to the PFS definition.
10 August 2020	Instruction for collecting hospitalization report and exams reports in case of serious adverse events section was updated. Switch to the approved Isatuximab administration mode with fixed volume. Option of direct supplies of oral investigational medicinal products (IMPs) was added in case of regional or national emergency declared by a governmental agency that resulted in travel restrictions, confinement, or restricted site access.
11 March 2021	Based on the positive interim PFS data, the treatment effect of IKd was expected to be better than initially anticipated in comparison to Kd. A descriptive PFS analysis was added when approximately 180 PFS events were reached. Based on more PFS events accumulated, this additional analysis would help to better characterize the distribution of PFS in a descriptive way for the IKd arm. With approximately 180 PFS events planned, the possibility of observing the median PFS time for the IKd arm was expected to be increased. Clarification of accidental or intentional overdose of isatuximab and carfilzomib was defined by each administration and dexamethasone defined by cycle. Appendix N was added for contingency measures for a regional or national emergency declared by a governmental agency.
14 September 2021	Addition of the possibility to omit carfilzomib dosing on Days 8 and 9 if a subject asked for a more convenient schedule and Investigator agreed because she/he judges that the maximum benefit was reached. If dexamethasone dosing was maintained on Days 8 and 9 while carfilzomib on Days 8 and 9 was omitted, possibility to re-increase the dose of dexamethasone if dose previously reduced, based on Investigator judgement.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34097854

http://www.ncbi.nlm.nih.gov/pubmed/36372355

http://www.ncbi.nlm.nih.gov/pubmed/36239134